I-RECOVERY KERNEL

Inombolo Yezincwadi Zocwaningo Lwezengqondo.

ΔFosB

IMOLIKHULI YOMHLOBANO.

Izinqubo, Ubunjiniyela, Ukuhlolwa, kanye Nesikhathi Sokuhlanzwa — Uhlelo Lwesibili.

⚠ UMTHOMBO WOKUNCIPHISA UBULIMAZI NENHLANGANISWA YOKUFUNDISA — AKUYONALO UKULULEKA KWEMIDLALO YOMDOKOTORI NOMA UKUHLOLELWA KWE-GENETIKI.

Ngeminye yezimo eziphuthumayo, shayela u-112 noma uthume umlayezo ku-0800 567 567.

Isiphuzu esikhulu ngaphambi kokuba uqale.

Lesikhathi sesibili lesi khasi, esandisiwe ngomkhuba omkhulu kakhulu wezomzimba, ubuchwepheshe bomhlaba-kazi obuqinisekisile mayelana nokuzinza kwe-ΔFosB (kunokusebenza kwezobungane bomhlaba-kazi ezitolo eziningi abantu abangakwazi ukuyohlola), ingxenye mayelana nokuthi ukuhlolwa kwe-DNA kanye nokuhlolwa kwe-epigenetic kungakaniphi okungenzeka ukuthi kutholwe, kanye nemibuzo emibili ebuza njalo ezihlangeni zokululama: kungani ukusetshenziswa kwezinto eziningi kungenza ukubuyela esimweni esijwayelekile kube nzima kakhulu, kanye nokuthi kungani ukuphindaphindi ukusetshenziswa ngemuva kokuxeshwa okuhle kakhulu kubuya ngokushesha kakhulu.

Imithethizo efanayo njengohlangothi lokuqala isasusebenza: I-ΔFosB akaze yahlaziywa ngokuqondile encibilikweni yomuntu ebukhoma. Konke ngomthamo wayo nokwehla kwayo kutholakala ezifundweni zezilwane, ezilinganisweni zama-gene ngamathuluzi, kanye nezifundo ezimbalwa zezingxenye zombili zokugula ezitholwe emithwini yabantu. Izikhathi zombantu lapha zikhulisiwe, futhi zibhalwe ngokucacile njengezikhathi ezikhuliswe. Lapho le ngxenye ithumela ukuzethemba kunengxenye yangaphambilini, akusona ngoba ukungaqiniseka kuye kwahlaziywa—kusho ukuthi ngoba isayensi esiyisisekelo yinde ngokucacile.

Ukuqinisekisa.

Izindingidi zobufakazi ezifanayo ezisetshenziswa kuso yonke inkulumo-mbhalo ye-Recovery Kernel zisebenzisa futhi lapha:

- KHONYANISIWE — ubufakazi obuqinile, obucindezelwe, nobonakalayo (njengobubona obuvame kakhulu ezifundweni zezilwane mayelana ne-ΔFosB; ububona bomuntu obonakalayo lapho kukhonjiwe).
- INANISO — idatha ebonakalayo futhi ehambisana, noma idatha ebonakalayo kanye nedatha ebonakalayo, ekhombisa ukuthi izinto eziningi zihamba ngendlela efanayo.
- EMERGING — okungenzeka, esigabeni sokuqala, kodwa akukona ukubonakala kukho ukubambisana.
- UBUNGANE LWABAMAKHULU/IZINHLELO - uhlelo olusetshenziswa kulolu hlelo lokuhlanganisa; landelwa njengokuthi yiphethini, hhayi iqiniso.
- CONTROVERSIAL/MIXED — kukhona ukungqubuzana/umxholo ohlukahlukene - kukhona ukungqubuzana ezincwadi.
- AKUQONAKALISI — kufakiwe ngoba abantu bayibuza, kodwa akukho ukufakazela okukhulu okusemandleni.

1. Yini i-ΔFosB empelini — Indlela, ngokugcwele.

[ESEKHISIWE] (izinhlobo zenyanga; le ndlela ethize iyiwumthombo ohlosiwe kakhulu ezincwadi zobufundisi bezinkomo ezihlobene neqembu lika-Eric Nestler).

I-ΔFosB iyindlela esondelelayo yengxenye ye-splice yegenesi ye-FOSB, futhi isebenza njengomthuthuzisi we-transcription—iprotein elenza amanye amajini asebenze noma ayeke ukusebenza—efinyelelwe kakhulu kwi-nucleus accumbens, dorsal striatum, kanye ne-hippocampal dentate gyrus. Isizathu sokuthi kuhlanganiswe kunokuthi kuguqulelwe ngemuva kokuchazwa ngakunye kuxhomekile kumicimbi emibili ehambisanayo yobuchwepheshe:

- Ukuhlanganiswa kususa umnyango wokupheka. Ngesikhathi esikhulu sokuthakaselwa, uchungechunge lomsiko (okuholela ekusebenzisweni kwe-dopamine D1 receptor, i-Activin/ALK4 pathway, kanye ne-SMAD3–PCBP1 protein complex) kubanga ukuthi i-pre-mRNA ye-FOSB ihlanganiswe ngendlela ehlukile kuleyo evamile. I-ΔFosB protein evela kulokhu ingaphandle yengxenye yesigceko esingemuva (C-terminal region) okuyinto i-FosB ephelele esebenzisa ukuthi izidalwe ngokushesha yi-ubiquitin-proteasome system. Ngaphandle kwaleyo ngxenye, i-ΔFosB ihlala isikhathi eside kuneprotein yayo oyihlo—kodwa isasengokuthile elula ekulahlekeni ngaleso sikhathi.
- Ukufakwa kwephosphate kuvala umnyango. I-Casein Kinase 2 (CK2), enjini esebenza ngokuqhubekayo emaqinisini, ifaka igumbi lephosphate endaweni ethile — i-Serine 27 — eduze nengxenye yangaphambili yephrotheni ye-ΔFosB. Lokhu kushintsha ukuma kwegeyini kulinganisa ukuthi iphrotheni ibe ngaphandle kwazo zonke izindlela ezisele ezangayilahlisa. Le ndawo efakwe i-phosphate iyisigaba esiqinile, esingu-35–37 kDa esiqala ukuphinda ngokuphindaphindiwe ngempumelelo

ngempumelelo ngemp

Ithebhithebhu elingezansi lixhumanisa umehluko oyingxenye yendlela lokhu okwenza.

Isoformu.	Mass ezingana yo cishe.	Yini enza ukuthi kube kanje?	Ukuhlehliswa.	Ukuhlala
Full-length FosB.	~50 kDa	Ugunyaza kokubili izindawo zokuqeda ekuphindweni lokuqeda kwe-C.	Ukuhlanganiswa okubukhoma kwe-ubiquitin ne-proteasome kwezindawo zokuqeda	Okumele - amahora

Isoformu.	Mass ezingana yo cishe.	Yini enza ukuthi kube kanje?	Ukuhlehliswa.	Ukuhlala
			ekuphahleni.	
Unphosphorylated ΔFosB	~33 kDa	Ukuguqulwa kwe-exon-4/intron-4 ngokuqeda ukuhlanganiswa kukhishwa izingxenye ze-C-terminal degron, kodwa i-Ser27 ihlala ingavikelekile.	Ukuhlazwa kwe-proteasome ngengxenye yangaphambili ebonakalayo.	— amahora ayisikhathi esincane kuya ngosuku olulodwa
Phosphorylated ("stable") ΔFosB.	~35–37 kDa	I-Casein Kinase 2 (CK2) iyashintsha i-Ser27, okuyinto ehlanganisa ukuguquka kwegeyini yale protein, okuyinto ekhuphula izindlela zokuhlehliswa ezisele.	Ukunqamuka ekuhlanzeni kwe-proteasome ngesikhathi efakwe ama-phosphate.	Kubekwa — kuhlanganisa kakhulu kule minyango eminingi, kutholakala amasonto ambalwa ngemuva kokuyekethwa kule minyango ezifundweni zezilwane.

Ok, ake: i-ΔFosB ayiqali ukuhlanganiswa ngoba kukhishwa kuyo kakhulu — ukukhiqizwa kwe-mRNA kuye ngempela kunciphile kancane lapho ukuchayeka kwezidakamisa kuyekile. Iyahlanganiswa ngoba, uma iqaliswe, iyeka ukuhlanekezwa ngesilinganiso esijwayelekile. Ukululama, ezingeni lamakhemikhali, kukuvela kakhulu ekulindeni ukuthi iphrotheni ekhiqiziwe ngokukhethekile ukuthi ingahlanekezwa ngokushesha.

2. Ukukhiqizwa kwe-ΔFosB kuyo yonke uhlu lwezinto ezisetshenziswa kwi-Recovery Kernel.

"Ukufakwa okuhlobene" kuhlola amandla adopaminergic, isivinini sokuqala ukusebenza, kanye nobunguqulo obuqondile bokugcwalisa kabusha - lezi zinto ezintathu ezihlanganiswe njalo ezincwadini zokuhlaziya ezifundwa ngamahlalakhubo mayelana nokuthi zingakanani izinto ze-ΔFosB ezilandela.

Izinto / Ukuziphatha	Imisebenzi eyinhloko ekhuthaza ukukhuliswa kwe-ΔFosB.	Ukufundisa okuhambisa nayo.	Ubufakazi.
I-alkohol.	Ukuguquka okunjulile kwe-GABA/glutamate kanye nokunyuka kwedopamine okuphindaphindeke ngenxa yokusetshenziswa okungokuhlukanisiwe.	Phezisi kuya kwephakeme (kuxhomekile kudose kanye nohlelo).	KHONYWA.
Cocaine	Ukubhaleka okubukhoma kwe-DAT; ukuphakama okukhulu nekubukhoma kwe-dopamine.	Phezulu.	KHONYWA.
I-crack cocaine.	Ifinyelela umzimba ngendlela efanayo ne-cocaine, futhi kutholakala ngokushesha cishe imizisi eyisikhombisa ngokusutha.	Kukhulu kakhulu — ukuba ngokushesha kunciphisa ukuba	KHONYWA.

Izinto / Ukuziphatha	Imisebenzi eyinhloko ekhuthaza ukukhuliswa kwe-ΔFosB.	Ukufundisa okuhambisa nayo.	Ubufakazi.
		ngokushesha kokuqalisa.	
I-methamphetamine.	DAT/NET ukubuyiselwa - ukukhishwa kwedopamine, hhayi nje ukuvinjelwa kokuthathwa kabusha.	Kukhulu kakhulu.	KHONYWA.
MDMA	Ukukhishwa okukhulu kwe-serotonin kanye nokukhishwa okulinganisiwe kwe-dopamine.	Ukulawula (ukutoxa kwe-serotonin kukhawulela imizuzu yokusebenzisa futhi).	MUNGABONAKALWA.
I-nicotine.	Ukuncibilika kwe-receptor ye-nicotinic okuhantsha ukutheleleka okuvamile (okuyikhulu kuya kwezinkulungwane ezingu-20 ngosuku).	Ubukhulu obukhulu buvuselela ukuntuleka kwamandla ngamathuba ngalinye.	KHONYWA.
I-heroin / ama-opioidi amele.	Ukuvuselelwa kwe-mu-opioid receptor kuphazamisa amaselula e-dopamine e-VTA.	Moderate–High	KHONYWA.
Fentanyl.	Ifinyelela umgudu ofanayo ne-heroin, kodwa unamandla amakhulu kakhulu futhi uqala ukusebenza ngokushesha kakhulu.	Phezulu.	MUNGABONAKALWA.
Benzodiazepines.	Ukukhuthazwa kwe-GABA-A; ukuntulelwa okungaqondile kwama-dopamine.	Phansi - Okungenani.	EMBUTHELWAKALA
I-cannabis (i-THC)	Ukusebenza kwe-CB1 okukhawuleza ama-neurons e-dopamine e-VTA.	Phansi - Okungenani.	EMBUTHELWAKALA
Ketamine.	Ukungqubuzana kwe-NMDA; imiphumela eholominezi ayenzi ukwanda okungaqondile njengokuthi izinto ezikhuthazayo.	Phansi - Okungenani.	EMBUTHELWANA
GHB.	Ukusebenzisana kwe-GABA-B; imiphumela yedopamine ayenzi ukushintsha ngqo futhi ihlukaniswe ngamazwi amabili.	Phansi - Okungenani.	EMBUTHELWANE
Kratom.	Ukusebenzisana kwe-mu-opioid okuyingxenye, ngamathuba aphezulu.	Phakeme kancane - phezukule (kuxhomekile kumanani).	EMBUTHELWAKALA
Mephedrone (4-MMC)	I-substrate-releaser eyuhlanganisiwe ye-DAT/NET/SERT, ifana ne-cocaine kodwa enesikhathi esifushane esiphelelayo.	High - impilo emfushane ihlelela ukuthi kudingeke ukutakazelwa kaningi.	EMBUKWAYO

Izinto / Ukuziphatha	Imisebenzi eyinhloko ekhuthaza ukukhuliswa kwe-ΔFosB.	Ukufundisa okuhambisa nayo.	Ubufakazi.
Methedrone (bk-PMMA / 4-MeO-methcathinone)	Ifulekelele kakhulu elingafana ne-mephedrone; umkhiqizo onamandla osele ukukhipha i-SERT futhi unomthelela omncane ku-DAT.	Kubukhulu obuyi-moderate kuya kokuphezulu - kunokumphumela omncane kakhulu kwi-dopamine uma kulinganiswa ne-mephedrone, kodwa ukufakazela okufushane kufanele kwenziwe kaningi njengoba kwenziwa ne-mephedrone.	UBuhlakani bomlobi/uhlelo - kutholwe ngokucwaningi ngohlu lwe-cathinone, akukho ucwaningo olunzulu olwenziwe.
Ukugembula / ukudlala imidlalo / eminye imikhakha yobungane.	Ifu elifanayo elenza ukuthi umuntu azizwe ukujabulela, kodwa kukhuthazwa ngendlela yokwenza izinto ezahlukene kuye ngokuthi ngabe umuntu ufinyelela umphumela ofanele noma cha, kunokuba ngempahla.	Ukubambisana okulingisiwe-phezulu nengxenye enkulu yabasebenzisi.	ESEKHISHO (izindlela zokuziphatha zezilwane, imiklomelo yendalo).
Ukudla okunambithekayo kakhulu / ushukela.	Ukudla okune-sikhathi esiningi esinezithambile nezamafutha ezinkulu kubonisa ukufana ne-accumbens ΔFosB efanayo nalokho okubonwa ezifundweni zezidakamizwa.	Moderate	MUNGABONAKALWA.

IMethedrone akukaze yibe yingxenye yocwaningo oluqondile mayelana ne-ΔFosB; ukufakwa kwayo kutholwe ngokuthi ingaba yingxenye yeqembu lama-cathinone, hhayi ngokwobubanzi bomlingo.

3. Izikhathi Zokugcwaliswa — Okuthi Idatha Ikubonisa Empeleni.

Akukho isikhathi esinqunyiwe sokukhuliswa kwe-ΔFosB esenzelwe umuntu ophilayo. Wonke umsebenzi ngaphansi uvela ezicini zombogo zezilwane noma ezifundweni ezimbalwa zabantu ngemva kokufa. Sebenzisa lokhu njengemaphu yobungqamuka obunzulu, hhayi njengeliqinisekiso lwesikhathi.

Ikhambu.	Ngingakwazi ukukusiza ngalokho.	Isikhathi esilinganiselwe.	Ubufakazi.
Ukukhuliswa okukhulu.	I-ΔFosB engaphazanyiswanga ivela ngemuva kokuba ngokushesha; iphansi kakhulu, cishe isuswe.	Amahora ayisikhathi esifushane, cishe usuku olulodwa.	KHONYWA.

Ikhambu.	Ngingakwazi ukukusiza ngalokho.	Isikhathi esilinganiselwe.	Ubufakazi.
Ukuzivumela.	Ukuthostwa okuphindaphindwayo kudalisa i-ΔFosB engenziwa yi-CK2, engunaphutha, eyagxiseka ekuhlikweni kwe-proteasomal futhi ihlala.	Kuthuthwa kule minyaka nemizuzwana yokusetshenziswa okuphindaphindiwe.	KHONYWA.
Ukukhulu kokuqokelelwa.	Ukuthostwa okuqhubekayo nokuphindaphindwayo kuqinisa ukungezwani kakhulu kunalokho okulahlekelwa.	Imizinsuku engu-2–4+ ngamanye amathuba, futhi kukhulu kakhulu; kuxhomekeke kumthamo/ubudlova.	MUNGABONAKALWA (ngamanye izilwane, kuye ngomthamo).
Ukuyekezwa kwe-mRNA ngemuva kokusetshenziswa okugcina.	I-FOSB entsha iyeka ukukhishwa cishe ngosuku olulodwa ngemuva kokuyeka - akukhiqizwa amaprotheni amasha.	~24–48 amahora	NGENAKUQONDILE (ilwandle)
Ukwehla kwe-protein.	ΔFosB esikhunyezwa ngaphambi kokuphazamiseka siyahlazeka kancane kwi-nucleus accumbens kanye ne-striatum, noma ukukhiqizwa kwayo kungayekile.	Amaviki ambalwa kuya ezinyangeni ezimbalwa ezifundweni zezilwane ezincane; kutholakala ezicathweni zombili emva kokufa, okubonisa ukuzinza kwayo.	IMBUZI (ngamanye amakhambi kanye nezivivinyo ezilandelayo zomhlalaphansi).
Ukuhlala / ukuhlala kwe-chromatin.	Ushintsho kwezinga lamakhambi adenele kanye nokuguqukuka kwe-chromatin (bheka uMgqobo 4) kuqhubeka ngaphezulu kukawo wonyango olufanele.	Kungathatha izinyanga ngemuva kokuthi kukhulunywe nge-ΔFosB efinyelelwe ezinhlotshweni zezilwane.	EMBUTHELWAKALA

Ukufundwa okunzulu: ukwehla okukhulu kakhulu kwi-phorotini i-ΔFosB ngokuvamile kwenzeka ezinyangeni ezimbalwa ngemuva kokuyeka ukusetshenziswa kwento ethile. Kodwa—futhi lena yingxenye eminingi emibhalo eyishiyelwe—ukuhlanzwa kwephorotini akufani nokubuyiselwa kwamasistimu. Le mpikisano iyisihloko sesigaba esilandelayo, futhi ibaluleke kakhulu kunazo zonke ezinye izinto kuleli khasi.

4. I-chromatin eyahlala kakhulu kuneprotein.

[KHONYWA] (izinhlobo zenyanga).

Ngenkathi i-ΔFosB iyasebenza, ayihlali kuphela kwi-nucleus—iyakuletha izimo ezilandelayo eziguqulela izingeni zamajini athile, futhi lezo zimo zihlala kakhulu kunale-ΔFosB ngokwayo.

- Kwezinjini, kuleyokucindezela, ezifana ne-c-fos, i-ΔFosB ibandakanya izindawo ze-AP-1 kumphromotha futhi ikhulethe i-Histone Deacetylase 1 (HDAC1). I-HDAC1 isusa

amaqembu e-acetyl ezindaweni eziseduze zeminwe yama-histone (i-H3K9), okwenza ukuthi leli gumbi ledna libambezeke futhi libe yinkinga. Igini liyathuleka—ukuntuleka okuhlala kude ngisho nangemuva kokuthi iphrothini ye-ΔFosB isusiwe.

- Kwezinjini, kusebenzisa:
  * CDK5
  * i-AMPA receptor subunit GluA2 (GRIA2)
  * ARC
  — i-ΔFosB ikhulethe i-BRG1, okuyingxenye ebalulekile ye-SWI/SNF chromatin-remodeling complex. I-BRG1 ivula i-chromatin kulezindawo, futhi umphumela olandelayo uyahlanganisa nokwanda okubonakalayo kwezintambo zedendritic ezibaluleke kulezinkampani zamaselula ezixhase ukujabulela.

Lena yinto enembile echaza okuthile abantu abathola ukululama kakade bayazi ngokwenzelweko: ukuthi umkhuba awufuni "ukuphela" nje ngoba ifiso elikhulu liye linyathezeka futhi iphrotheni ekhuthazayo kulo liye, ngokuyisisekelo, liye lwehla. Isakhiwo sezingqondo sebilungiselelwe kabusha ngokwangempela — nezintambo eziningi, ukuguqulelwa kwe-receptor okuhlukile, uhlaka oluhlukile lwe-chromatin kumajini athile — futhi lokho ukulungiselela kabusha kuyingxenye esheshayo, ende "yokubuyela esimweni esijwayelekile". Futhi kuyisihloko esiqondile sezigaba ezingu-8 no-10 ngenhla.

5. Izinto ezilawula ukuguquka - Yini eyilungele futhi yini eguquka kakhulu.

Konke okuku-Section 2 kukhuthaza ukwandisa kwe-ΔFosB ngokusebenza kwezinkundla zokuthumela eziguqukayo—ukuphakama okukhulu kanye nokwehla kwezinto ezisebenzisa izikhathi eziningi, okugcwele. "Izinto ezilamula," ngomqondo osetshenziswa lapha, yimithi kanye nezinto ezibalulekile zokudla ezilawula lokho kukhuphuka nokwehla ngokuyimisela, noma ezisekela indawo yebhayoloji ezungezile ngaphandle kokuthinta ngqo indlela yokukhiqiza. Akukho ngisho yini kuleli gidi eliphindaphindaphile ukwandisa kwe-ΔFosB okusekho—akukho okungenzi lokho ngokushesha kunesikhathi. Okungenziwa ngempela yilezi zinto ukugwema ukwandisa kwayo, noma ukugcina izinhlelo eziseduze (ukukhiqizwa kwe-dopamine/GABA, umsebenzi wama-enzymes oxhomeke ekufakelweni) ukuthi kungaba umthwalo owengeziwe ngesikhathi sokululama.

Imithi yezinkinga zengqondo — Yini ephindaphindayo ne-ΔFosB pathway, kanye nalokho engiphindaphindayo?

Kuyimibuzo eyiqiniso futhi enengqondo: imithi ethile yezokwelapha engqondweni ihlaba izindlela ezifanayo namakhemikhali ase-thebula le-Section 2, futhi impendulo eqotho ukuthi kukhona uhla, hhayi "yebo" noma "cha" kuphela.

Ukuhlukaniswa Kwemithi	Ifinyelela ngendlela efanayo.	ΔFosB Relevance.	Ubufakazi.
Imithi yokulalisisa (ikakhulukazi izivalo zokuqala ze-D2, njengohaloperidol).	Akuyona into ebekwe kwiSigaba 2, kodwa ukubanjwa okuphansi kwe-D2 receptor okuhlala kuphansi kuholela ekuguquleni kwe-striatum.	Ukwelashwa ngokungapheli kudalisa ama-complexi a-ΔFosB-like e-AP-1 asezingeni elilinganisiwe esifungweni esibhalwe (striatum) ezifundweni zezilwane - okubangelwa ngobudlova futhi kubandakanyeka ngokwengxenye ekuthuthukeni kwe-tardive dyskinesia, okuyinto ehlukile kodwa ehlobene nendlela yokuzivumela esikhathini eside.	INGXENI (yezilwane)

Ukuhlukaniswa Kwemithi	Ifinyelela ngendlela efanayo.	ΔFosB Relevance.	Ubufakazi.
Imithi ekhuthazayo (methylphenidate, ama-amphetamine salts).	Ifinyelela efanayo ne-DAT/NET efana ne-methamphetamine engumuthi ongahlalwa (Isigaba 2).	Ukukhuthazwa okunengxenye yobungcweti - kodwa ukuthatwa kwezindlela zokwelapha (eziningi, ezihlala isikhathi eside, kanye ngosuku) kugwema ukukhuluza okukhulu okubonakala kukhuthaza kakhulu. Ingxenye yangempela yokunganekhona ingaba ephansi kakhulu kunokuthatwa kwezindlela ezingafanele, kodwa ayikhuliswa.	EMERGING — indlela yokusebenza, izinga elingacacile.
Ukwelashwa ngamakhambi afana ne-methadone ne-buprenorphine.	Ifu elifanayo ne-opioid receptor njengohijini (Isigaba 2).	Lokhu kuyincazelo yangempela yencazelo "yesithambisi": ukuba nomjikelezo omude kanye nokwelashwa okuqhubekayo kenzelwe ukugwema ukuguquka okukhulu okubangelwa ukwelashwa okuyisikhathi. Kungaba yingxenye enkulu yokuthi i-OAT (opioid agonist therapy) ibhekwa njengendlela yokwelapha esebenza futhi esesikhathini, kunokuba yinto eqhubisa ukwezwa.	OK.
Benzodiazepines (okwelashwe ngayo, ukusetshenziswa kwephilisi elide).	Ifinethi ye-GABA-A ebalulwe njengezinto ezincane kakhulu kuze kube yisilinganiso esiphakathi kwiSigaba 2.	Ukusebenzisa ngokuphindaphindiwe kudala ukuthemba okwangempela emzimbeni kanye nokuzamazama okunzima uma uyeka ukusebenzisa — kodwa lokhu kuhlaziywa kabanzi ngokuthi kudalelwa ukwehla/ukutolozana kwe-receptor ye-GABA-A kunokuba ukukhona okukhulu kwe-ΔFosB.	EMBUTHELENI
SSRIs / SNRIs	Akuyona into ebekwe kwiSigaba 2 — ukuvimbela ukuthathwa kwe-serotonin/norepinephrine.	Ukwelashwa ngamakhambi okwelapha ukudangala okwedlule kukuholela ekukhuliseni kwe-ΔFosB ezifundweni zezilwane - kodwa kwi-hippocampus kanye ne-frontal cortex, hhayi kwi-nucleus accumbens, endleleni ekhombiswe ukuthi isekela ukuguquka kwengqondo okwelapha. Kufanele ibe cishe eduze nenqubo "yokuvikela" ebanjelwe ukudlala (Isigaba 15) kunenqubo yokutadela. Ukwehlukana kwamakhambi okwelapha ukudangala kungaba yinkinga, kodwa ngamathuba okuguquka kwezikhathi zokwamukela, okungahlobene ne-ΔFosB ye-accumbens.	EMERGING (ukuqala); ESTABLISHED (izimpilo ezilandelayo zikhona, uhlelo oluhlukile).

Akukho nto eyenzi ukuba uyeke ukutshala izindlela zokwelapha ezibalulekile zengqondo, futhi lokhu akuyona incazelo yezokwelapha. Izindlela zokwelapha ezilwa nezinkinga zengqondo, izindlela zokwelapha ezithuthukisa ukuzimisela, ukwelashwa kwezindlela zokwelapha ezithintekayo, izindlela zokwelapha ezithintekayo, kanye nezindlela zokwelapha ezilwa nokuduka, zonke zinezinkinga ezithile ezibalulekile - ezinokuba yizinkinga ezinkulu kwezempilo - ezikhona, kungakhathaliseki ukuthi i-

ΔFosB ibalulekile yini. Noma yiluphi ushintsho kuluhlu lwezindlela zokwelapha zokwelapha izinkinga zengqondo kufanele kuthathwe umeluleki owayelapha, njengoba ukuyeka ukutshala izindlela zokwelapha ezithintekayo noma izindlela zokwelapha ezilwa nokuduka ngendlela engenakudluliselwa kufanele kubhekwe njenginqubo yezokwelapha, hhayi into okumele uyenze ngokuzimisela.

Ama-cofactor ezakudla.

Akukho kuthathu kwalezi zinto ezintathu eziyindlela yokudla okuhloliwe ngokunqamuleka ku-ΔFosB ngqo. Kuhlala kunento eyodwa, eyaziwe ngokuhlukana, ebalulekile kule ndawo yezicini zasebuchwadini leli elisebenza kuyo—amandla okukhiqiza i-dopamine/GABA, kanye nokwaneleka kwe-MTHFR/MAOA cofactor (Isigaba 6, Izinga 4)—ngaphandle kokuba kwaziwe ukuthi yenza ukuthuthukiswa kwe-ΔFosB.

I-nutriyenti.	Indima esetshenzisiwe.	Plausible Link to ΔFosB
P5P (Pyridoxal-5'-Phosphate — i-B6 esebenzayo).	I-cofactor ebalulekile ye-AADC (eyaguqula i-L-DOPA ibe yidopamine, kanye ne-5-HTP ibe yiserotonin) kanye ne-glutamate decarboxylase (eyenza i-GABA). Ukuba khona kwe-B6 kubalulekile kakhulu ekuguqulweni kwe-dopamine kanye ne-GABA.	Ukuba kunamandla amaningi okukhiqizwa kwe-dopamine, kungase kube ukuthi kunamazwi amaningi afika ku-cascade ye-D1/PKA/CREB eqala ukubhala i-FOSB (Isigaba 6, Izinga 3) — lokhu kuyinkomba esuselwe kubucwaningo bemibimu, hhayi umphumela obukisiwe. [OKUFIKILE, okungahleli.]
R5P (Riboflavin-5'-Phosphate — i-B2 esebenzayo / i-FMN)	I-cofactor yama-enzayimbi ezingama-flavoprotein, okubalwa kulo i-MTHFR (ebalulekile ikakhulukazi kubagwebi be-C677T, lapho i-enzayimbi yabo ibalulekile kakhulu ekushisweni kanye nokuxhumene ne-FAD) kanye ne-MAOA.	Amanyathelo amabili aphakhe kwi-ΔFosB - isimo seriboflavin senza ukuthi i-MTHFR ne-MAOA zisebenze kangakanani, futhi lezi zinzwa sezivele zinobubanzi obuncane, obungatholakali ngqo, kwi-ΔFosB (Isigaba 6, Izinga 4). [KUVELE, okungahleliwe]
Calcium Glycinate.	Inikeza i-glycine (isicibilisi sezimbunguzo kanye nomkhiqizi oyimpoqo we-NMDA receptor). Ukungena kwe-calcium ngama-NMDA kanye namachanneli agxile kuvoltaji kuguqulela ku-CaMKII.	CaMKII iyindlela yokufaka ama-fosfate ehlukene ne-CK2, okuyindlela yokufaka ama-fosfate eyenza ukuthi i-ΔFosB ifakwe ama-fosfate ku-Ser27 (Isigaba 1) futhi iyasebenza ngokuqhubekayo kunokuthi isetshenziselwe ukukhishwa kwe-calcium. Akukho mkhakha onokugunyazwa ngokwengqondo oxhumana nezinqubo zokusebenza ze-ΔFosB ngokukhethekile. [AKUHLANGANISWA].

Ukuhlela okunzayo: lezi zinto zisekele ukusebenza okujwayelekile kwezicubu zombili, kungakhathaliseki ukuthi umuntu ukhona kuphi kuleli θuba le-ΔFosB elichaziwe kuSahluko 3 - hhayi ngoba kukhishwe ukuthi zishintsha leli θuba, kodwa ngoba i-dopamine, i-GABA, kanye nezinhlelo zama-enzymes ezixhomekile ekufakelweni kubalulekile ngokwayo, ngaphandle nangaphandle kwengxenye yendlela yokuphuza izinto.

6. Ubucwaningo bomhlaba wonemandla kanye nokuhlaziywa — Izitekhisi ezine zobufakazi.

Ubuhle bomlando bokuhlazwa kwe-ΔFosB uhlukaniswa ngamazinga amane, kusukela kububanzi obuqinile kunawo kokuphansi. Kubalulekile ukuthi isikhathi esithile sitholakala ngaphansi kwenzipho enjani, ngoba ubufakazi obuqinile buwabadala abantu abangazithola

ngendlela yemvelo futhi ayiwa yizivivinyo zokuhweba — kanti izinzwa abantu bangazivivinya zihilele kude kakhulu nendlela yokusebenza.

Izinga 1 — Ukuguqulwa Okubukhoma, Okwenziwe Ngokungathíthatwa ku-FOSB Ngokuzithoba.

Lesi yisibonakaliso esiqinile kakhulu kulo msebenzi wonke, futhi sitholakala ekulethweni kwe-gene ngokusetshenziswa kwe-viral vector ngqo e-nucleus accumbens yezilwane ezincane - hhayi ekuguqulekeni kwe-human okwenzeka ngendlela yemvelo.

Variant	Yenza okuthile.	Impumela ekuhlanzeni.	Ubufakazi.
FOSB Ser27Ala (S27A)	Ukuguquka kwe-point eshintsha i-serine ngomuthi ku-alanine endaweni yesikhathi 27 — i-CK2 ngokwengeziyo ayikwazi ukufaka i-phosphate emuthi.	Kuvimbela ngokuphelele ukufakwa kwephosphate okuzivikela; ezifundweni zokusebenzisa ama-viral vector okuletha leli dolobha eliguqukile e-nucleus accumbens, ukuhlazwa kwe-ΔFosB kukhulisa kakhulu futhi ukwazeka kokuziva okwedlule kuncishisiwe kakhulu.	KHONYWA (ilayini, eyenziwe ngobunjiniyela).
FOSB Ser27Glu (S27E) — phosphomimetic.	Shintsha i-serine nge-glutamic acid, okwenza ukuthi ifane nomthwalo omkhulu ongokwemvelo owenziwa yiphosifate — iphrothini iyasebenza njengokuthi ifakwe ngaphakade ngephosifate.	Ihlanganisa ukubunjwa okuzinzile ngaphandle kokudinga i-CK2. Gcina ukuzinza okwedlule kanye nemiphumela ehlala isikhathi eside.	KHONYWA (ilayini, eyenziwe ngobunjiniyela).
FOSB exon-4/intron-4 splice-site variants.	Phasela ukubindwa kwe-PCBP1/SMAD3 okukhombisa ukuguqulelwa kwe-splicing.	Ukuguqula ukukhiqizwa kwe-transcript kuya ngemuva kwe-FosB egcwele, egcina i-degron, okuyinto esuswa ngokushesha — i-ΔFosB engunaphumezelo ayenziwa kakhulu.	MHLABA (izilwane)

Tier 2 — Ama-gene athweswayo ezindleleni zokuguqula.

Leji jini layafakazela ama-enzayim kanye namapurothini e-splicing-complex ahlanganisa i-ΔFosB. Ukuhlukahluka okuyingxenye yobuntu kulezi jini kungase kube nobubudlova, kodwa akukahlolwe ngokuqondile mayelana nezilinganiso ze-ΔFosB abantu—kuphela okudalwe ngohlelo.

I-gene.	Umsebenzi.	Impumela ekuhlanzeni.	Ubufakazi.
CSNK2A1 / CSNK2B (amayunithi okukhiqiza kanye namayunithi okulawula e-CK2).	Encode ukuthi yikuphi i-kinase ephosphoryliza i-ΔFosB ku-Ser27.	Ukuphansi kakhulu kwe-CK2 kudalela i-ΔFosB ukuba yibe ngumthombo ongenayo i-phosphate, okwenza ukuba ibe yinto ebuthini kakhulu — okungenzeka ukuthi kusetshenziswa ngokushesha.	MHLABA (izilwane, okuhlobene nomshini).
PCBP1 / SMAD3	Dala ikhompleksi yenukliasi eholisa ngokushesha ekuhlelweni kokuqanjwa kokuphindaphindwayo okukhiqiza i-ΔFosB.	Ukuguquka kwe-DNA okubangela ukuthi umzimba ungasebenzi kahle kuguqulela ukukhiqizwa kwe-mRNA, okwenza ukuthi kukhuliswe ukukhiqizwa kwe-FosB egcwele,	MHLABA (izilwane, okuhlobene nomshini).

I-gene.	Umsebenzi.	Impumela ekuhlanzeni.	Ubufakazi.
		kancane kancane kunciphisa ukukhiqizwa kwe-ΔFosB esilungele ukusetshenziswa.	
ACVR1B (isikhathi esiyisitorekisi se-ALK4).	I-receptor ephezulu kwe-SMAD3/PCBP1 splicing complex, eyasetshenziswa ngemva kwe-dopamine D1 signaling.	Ukwehliswa kwemitophoni kunciphisa ukuguquka kokuhlanganiswa kuya ku-ΔFosB — okuyisici esibalulekile esifana nomjantshi ngale ndlela efanayo.	EMPUZANA (yezilwane, yomshini)

Tier 3 — Izimpande ze-neurotransmitter ezisendaweni ephezulu.

Lezi yimiphumela yangempela ehlanganiswe namajini abantu — kodwa izifundo ezisemuva kwale miphumela zayilinganisa ukukhulu kokuphoxeka, ingozi yokubuyela ekusetshenzisweni, noma ukukhulu kwe-catecholamine, hhayi i-ΔFosB ngokwayo. Ukuxhumana ne-ΔFosB ngokuqondile kuyinkinga elungile esetshenziswa ngezinto ezitholiwe, hhayi umphumela oqondile. Funda ikholomu ethi "uxhumano olushiwo" ngobuqotho:

I-gene / Ukuguquka	Umsebenzi.	Ukuxhumana okuthiwa no-ΔFosB.	Ubufakazi — Funda ngesikhathi.
DRD1 (isivikelo se-dopamine D1) amapholomɔ.	I-D1 signaling idlala indima ekuguqulweni kwe-PKA/CREB okwenza ukuthi kuqale ukukopishwa kwe-FOSB.	Izinhlobo ezibonakalayo kakhulu zikhulisiwe ukukhulisa ukusebenza kokuqala kwe-transcription, okwengeza kakhulu izinto ezidingekayo ngendlela yokuhlanganiswa.	IMISEBENZI EKHULIWE — ukucwaningwa okungenzeka okuyisisekelo, okungalungiswanga ngamazinga e-ΔFosB abantu.
CHRNB2 rs2072661	Ukuguquka kwe-3' UTR ngaphakathi kwejini le-nicotinic receptor subunit, okuxhumene ezifundweni zabantu nokukhuluphala kokuphoxeka kwe-nicotine kanye nenqubo yokubuyela emuva.	Kuhloniphekile ukulungiselela ukushintsha ukusebenza kwe-cholinergic ekukhishisweni kwe-dopamine emthonjeni we-mesolimbic, okwenza ukuguqulela ukukhiqizwa kwe-ΔFosB.	IMISEBENZI EPHUMLO - izifundo zabantu ezichazwe zingaxwayisanga ukukhulu kokuphathalala kanye nenqubo yokubuyela emuva, kodwa ukuthi kungumphumela we-ΔFosB; ukuxhumana kwe-ΔFosB kuyinkomba, hhayi ukulinganisa.
DBH rs1541333	Ukuguquka kwe-dopamine beta-hydroxylase, okuguqula i-dopamine ibe yi-norepinephrine.	Kuhloniphekile ukushintsha ukulingana kwedopamine/norepinephrine ezindleleni zokugubha, okushintsha izinga lokukhiqizwa kwe-ΔFosB.	IMISEBENZI EFANA: okufanele kwaziwa ukuthi ucwaningo oluqoki luyilinganisa ukukhishwa kwe-catecholamine kanye nomfanekiso wokuthemba, hhayi i-ΔFosB ngqo.

Tier 4 — Uhlu lwe-gene olusebenzayo lwezabasebenzi.

Lezi zinzwa ezifakiwe yitestu yangempela ye-DNA yomthengi (idatha "eyisiko" ye-23andMe, noma iphaneli ekhothiwe kwenye indawo kuleli khasi le-Recovery Kernel). Akukhobunye yalezi zinzwa eziseduze kakhulu nenqubo—zikhona kanye, ngamanye amathuba kabili, kude nanoma yini ethintana ne-ΔFosB ngqo.

I-gene.	Yenza okuthile.	Noma ngabe.
COMT	Ibhubha ama-dopamine/norepinephrine, ikakhulukazi kwi-prefrontal cortex. I-Val/Val = ukuhlanzwa okushesha; i-Met/Met = ukuhlanzwa okubambezelekayo.	Akukho ulwazi oluqondile. Ukuxhumana okungenani okungatholakali ngokuqondile ngohlobonjabango lwesiginali se-dopamine. [UBUNGANE/UHLELO LOMBUZI]
MTHFR	Kulawula ukuguquka kwe-folate kanye namandla okuguquka emzimbeni wonke.	Akukhonanjalo uxhumano olubonakalisiwe nobudlelwane no-ΔFosB degradation. [AKUHLUTSHUNYEWE]
OPRM1 (A118G)	Lushintsha ukubandakanyeka kwe-opioid receptor.	Ngokungathangi kakhulu kokuqala kokuphimiswa kwe-opioid; akuhlobene nokuhlazwa kwe-ΔFosB. [OKUFIKILE.]
GABRA2	I-subiyunithi yomthunzi we-GABA-A; ihlobene nomngo wokuba umuntu ube nezinselele zokuthanda utshwala.	Umthombo onokungenzeka oholela ekuntulelweni kwe-dopamine okubangelwa ukusetshenziswa kwasilima. [OKUFIKILE]
FAAH (C385A)	Iguqulela i-anandamide; i-allele ye-A ikhombisa ukukhuthazwa kwebanga eliphezulu le-endocannabinoid.	Umthombo ongase futhi ube nomthelela obukhulu ekuzuziseni okuhlobene nokusetshenziswa kwe-cannabis. [OKUHLANGANISIWE]
MAOA	Iguquka i-dopamine, i-serotonin, ne-norepinephrine.	Umphumela ongase ube mbalwa ovela ekuhambeni kokuhlanzwa kwamayini. [UBUNGANE/ULWENZI LOMHLANGANO]
SLC6A4 (5-HTTLPR)	Ijini le-serotonin transporter; kuxhumekile nokuphimiswa kwezinkinga ezihlobene nokucindezelwa ezifundweni eziningi.	Akukho ubufakazi obudubula lokhu kuxhumana phakathi kwaleli jini kanye nokuguquka kwe-ΔFosB. [AKUQONAKALISI].
ALDH2	Iguquka i-acetaldehyde evela ekuhwebeni kwasilima; ukuguquka okungasebenzi kubangela ukuba umuntu ube nomswakama.	Kuyathinta uhlelo lokuthathe iziphuzo, hhayi i-ΔFosB ngokwayo. [UBUNGANE/INGXENYE YENHLANGANISWA, okungahleli.]
CYP2D6, CYP3A4, CYP2C19, CYP1A2, CYP2C9, CYP2B6	Ama-enzayimthi ehlisa izinga ledokumenti elisemzimbeni elisuswa ngokushesha emzimbeni.	Qinisekisa ukuthi umuthi ususukile emzimbeni, hhayi ukuthi ukuthi i-ΔFosB isukile yini ebuchosheni. Umthelela oyingxenye kuphela. [UKUHLOLWA KWEZINHLONIPHO/IZINHLELO, ngokuqondile]
HNMT	Ukuhlakazwa kwe-histamine.	Akukho zindlela ezimele zokuholela ku-ΔFosB noma ekuhleleni okubalulekile kwezinto ezijabulisayo. [AKUHLANGANISWA].

Akukho ukuhlolwa komchobo okutholakalayo namuhla okwazisa ukuthi kuzothatha izinto ezingaki ukuze igumbi le-ΔFosB eliyingxenye yomuntu ngamunye lihlale. Lokho kuyiqiniso. Kodwa lokho kuyisitatimende mayelana nalokho okutholakalayo emakethe, hhayi umkhawulo walokho okungenzeka. Uhlelo oluhlanganisiwe oluhlanganisa ukuphinda ukuhlolwa kwe-FOSB kanye nezinto ezilandelayo ezithinta ukusebenza kwayo (CK2, PCBP1, SMAD3, ACVR1B), idatha

yokufakelwa yonkana yama-genome, kanye nokulandelela kwezimpawu ezifanele ngokuhamba kwesikhathi ngesikhathi umuntu engaphandle kokuziphakamisa, kungase, ngokomthetho, zisondise kakhulu ithimba locwaningo ekulinganisweni eliyingxenye yomuntu ngamunye. Akekho okushicilele noma okuhlolwe ngokwesimboni ngalolu hlelo oluhlanganisiwe - kudinga izinhlelo eziningi ezihlukile zokuhlolwa. Ukusebenzisana kanye nomklamo olandelelayo, hhayi nje isethi eyodwa. Lokho kuyinkinga yokutholakala kwezinto kanye nokuvumelana, hhayi umthetho wemvelo. Umuntu onokudlala okufanele, imali, kanye nokuzimisela angakwenza lokho.

7. Ukuhlolwa kwe-DNA kanye nokuhlolwa kwe-Epigenetic — Yini Ongayithola Manje.

Ukuhlolwa Okujwayelekile (ama-SNP Arrays).

Ukuhlolwa kwe-DNA yabasebenzisi (uhlobo olusebenzisa izindlela ezifana neze-23andMe, noma iphaneli esetshenziswa kwenye ingxenye yalesi bhuku) uhlola izindawo ezithile ezaziwe zama-single-nucleotide kuso sonke uhlaka lwe-genome - okubalwa kuzo nezintshonalanga zeTier 3 neTier 4 ezithelwe kuthebula engenhla. Akuholi ukuhlolwa kwe-FOSB ngokwanele ukuthola izinguquko ezivamile noma ezintsha, futhi akakwazi ukuthola izinguquko ezakhiwe zeTier 1, ezingabonakali ngendlela yendalo kubantu. Kusebenziseka kwezintshonalanga ezifakiwe; akwakhiwe ukuthi uphendule le mbuzo ethize.

Ukuhlaziywa Kwenhlanzeko Ephelele Ngokusetshenziswa Kwebhisulfite (WGBS).

[ESEKHINI] uma kuhlala kule mbuzo ethize.

WGBS iyindlela yokufaka izingcezu zedatha (sequencing) ebonisa ukubekwa kwe-DNA methylation—isendlalelo semaki yobungane—kuyo yonke i-genome, kunokufundwa nje kwamakhambi e-genetic athile. Izinguqulo ezinkulu (ezivame ukuthengiswa njenge-"WGBS 30x," okubhekisa ekufafazweni okungenani okuyi-30-fold) zinikeza imephu efinyelelekayo futhi ethembekile ye-methylation. I-Sequencing.com manje isikhombisa umkhiqizo we-WGBS-30x njengelinye yezindlela ezincane kakhulu zokuholela lolu hlu lwedatha lwe-genome-wide ye-methylation kumakhasimende, kunokuthi ngohlelo lwezilabhu ezifundwa ezikhungweni zemfundo.

Ukuthi yini okungenzeka ukuthi ikwazise: amaphethini okubhujiswa yizinto ezisekelwe ekuhlolweni kwe-"epigenetic clock" (ukulinganisa ubudala bomzimba kusukela ku-DNA egazi), futhi ukuchoboza okuphazimekayo kuxhumene nokuguquka okubonakalayo kokubhujiswa ezifundweni ezisekelwe kugazi. Okungenzeka ukuthi kungakwazi ukukwazisa njengamanje: akukho mbiko obuyekeziwe, ogatshiwe ongenza ukufunda ukuguquka kwe-ΔFosB-specific chromatin state - ukuguquka kwe-HDAC1/BRG1 okuchazwe kuSection 4 - kusuka kwasampula legazi noma lomenzi. Lokho kuguquka kwenzeka kumaselula e-nucleus accumbens, okungatholakali ukuze kuhlolwe kumuntu ophilayo. Umphumela we-WGBS namuhla unikeza idatha yangempela, ehambisanayo mayelana nobhujiswa kuyo yonke i-genome; njengamanje, ayihumushishi. ukubuyekeza kombiko womuntu ngamunye we-ΔFosB, noma kungcono kangakanani idatha yangempela.

WGBS ingelinziswa njengemininingwane elingenziwe yomuntu osiza ukwakha umbono omude nezindlela zokuguquka kwempilo yakhe. Futhi, kuyindlela engabizi kakhulu yokuthola le mininingwane. Kodwa, ungacabangi ukuthi ireporti yanamhlanje izokunikeza inombolo ethi "amasonto ayizayo ukuze u-ΔFosB yakho ihlalele." Leso sindo sokuhumusha alikho okwamanje, kunoma ubani, nganoma yimiphi imilingo.

8. Ukusetshenziswa kwezinto eziningi kanye nokubuya okunzima kakhulu esimweni esijwayelekile.

[UBUNGANE/UKWENZANI KWE-AUTHOR/SYSTEM] ngokusekelwe kokuqinisekiswa kwezindlela kanye nemininingwane yeziphumo zokwelapha.

Abantu abaphulukile ekusetshenzisweni kwezinto eziningi bahlala babuyela esimweni sabo
esijwayelekile kancane kakhulu futhi ngendlela eyinkimbinkimbi kunabanye ngaphakathi kwe-
Recovery Kernel. Kukhona isizathu esisetshenziswa kwezinto eziningi kanye nesizathu
esisetshenziswa kwezinto eziningi kanye nesizathu esisetshenziswa kwezinto eziningi kanye
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- Ukuhlangana kokuhlanganyela. Cishe yonke into etholakala kuthebhili elingxenye yesigaba sesi-2 ihambisa ukukhula kwe-ΔFosB ngendlela efanayo — ukukhuthazwa kwedopamine ekuphathini eliyindaweni yokuqonda (nucleus accumbens) — nakuba zifike lapho ngezindlela ezihlukene (ukuvinjelwa kwe-DAT, ukusebenzisa ama-opioid, ukukhuthaza i-GABA-A, njll.). Ukusebenzisa eziningana kulezo zinto ngesikhathi esisodwa akudaleli amabhizinja afanele, ahlukene; kunalokho, kukhuthaza ibhizinja elikhulayo elisuka ezindleleni eziningi ngesikhathi esisodwa, okungase kudale ukukhula okukhulu futhi okushesha kunalokho okungaba yilono olulodwa kuphela.
- Ukuguquka kwama-chromatin alandelana. Izinto ezihlukene ngeke zihlanganiswe nezilungu ezifanayo ezisemthethweni ngemva kwe-ΔFosB. Izinto ezithusa, ama-opioid, kanye nomuthi onamandla ngalinye linomlingo ohlukile olandelwayo obhalwe kwi-literature mayelana nokuzithinta. Ukusetshenziswa kwezinto eziningi kungenza ukuguquka kwama-chromatin kube banoma yikuphi (Section 4) ezilungu eziningi nezikhungo, okwenza ukuguquka okukhulu okudingeka ukuphumelela, hhayi nje ukwandisa umthamo wesikhungo esifanayo.
- Imiphumela yezokwelapha ebabongiwe. Ngaphandle kokuthi yini enye esenzakalweni, ukusetshenziswa kwezinto eziningi kuhlala kuhambisana nokugcinwa kokuphathwa okubi, izilingo ezinkulu, kanye nokukhipha izinto emzimbeni okunzulu kakhulu kunokusebenzisa into eyodwa kuphela, njengoba kuboniswe ezincwadini zezokwelapha. Le ndawo inguqulwe kakhulu kunomkhuba wokusebenza kwe-ΔFosB—kungumphumela osemqoka, noma ukungabi nani ukungenelela kwezinto ezincane.

Akukho okusho ukuthi ukululama ekusetshenzisweni kwezinto eziningi akuyona into engenziwa —uhlelo lwe-Recovery Kernel lukhona ngqo kulabo abahlezi kakhulu. Kusho ukuthi izikhathi zokululama ezihlukaniswe ngolwazi oluhlukile (okubalwa nakuleli khasi lesi-3) kufanele kufundwe njengomkhakha oncane, hhayi umkhakha ophezulu, kulomuntu osebenzise izinto eziningi ezihlukene.

9. Ucwaningo - I-Trinity ye-Chemsex (Meth, Cathinones, GHB)

Ukusebenzisa izidakamizwa ezibizwa nge-"chemsex" - okuyikhona ikakhulukazi i-methamphetamine, ikathionine efana ne-mephedrone ("cat"), kanye ne-GHB/GBL, ngamanye ahluzo ne-MDMA noma i-ketamine - liyacoshwa njengezinto ezinzima kakhulu ukuyeka, ngabantu abayisebenzisa kanye nezinsizakalo zokwelapha. Isithombe sezakhamuzi kulolu mbhalo sichaza izingxenye ezibalulekile zalokho, nakuba hhayi konke.

Uphizi.	ΔFosB Induction (kusukela kuSahluko 2)	Indima eNgcwele eNkosini.
I-methamphetamine.	Kukhulu kakhulu.	Ukuguqulwa okukhulu kakhulu kwe-dopamine kulolu hlu lwezinto — ukuguqulwa kwe-DAT/NET kukhulisa ukukhishwa kwe-dopamine ngqo, hhayi nje ukuvinjelwa kokuyisongela.
Mephedrone / i-cathinones ("cat")	Phezulu.	Impilo emfushane kakhulu idinga ukuthi uphinde uthathe ubulungiswa obukhulu ngesikhathi esisodwa, okuyinto esenza ukuthi uqaphele kakhulu.
GHB / GBL	Phansi - Okungenani.	Umfanekiso omncane we-ΔFosB ngokwayo — ukubaluleka kwalo kulolu hlangothi luhlukile, luhlobene nokuxatshuzwa ngokomzimba (bheka isaziso esingaphansi), hhayi ohlelweni lokujabulela.

Ngokuhlukana, kuphela imithi emibili kwezintathu ebanjwa njengokuthi zenza ukukhuthazwa okukhulu kwe-ΔFosB. Okwenza ukuthi ukuhlanganiswa kubube kakhulu akuyona ukuthi wonke amaphuzu anquma ukusebenza okufanayo—kodwa ukuthi izinto eziningi ezihlukene zokuhlanganiswa ezivela ehlwini elidlule kulolu mbhalo zihlanganiswe ngasikhathi esisodwa:

- Ukuhlangana kwempumelelo kwe-dopaminergic (Isigaba 8) — imethu kanye ne-mephedrone zithinta izindlela ezifanayo ze-dopaminergic ngasikhathi sinye kunokuthi ngendlela eyi-seqenshal.

[ESEKHISI] Ukuxhumana ngokomzwelo ngokwawo yindlela ekhudlile yokukhiqiza i-ΔFosB, hhayi nje isimo esingokomzwelo. Izifundo ngezilwane (Pitchers et al., 2010, kusuka eqoqweni elifanayo elilokhu lutholile ukusebenza kwe-ΔFosB) zithole ukuthi ukuba nomzwelo kuphela kubanga ukukhula kwe-ΔFosB kwi-nucleus accumbens, VTA, kanye ne-prefrontal cortex - futhi, okubalulekile, ukuba nomzwelo kungenza izilwane zibe nezimpilo ezithile ezibangela ukuthi zithande ukuziphatha ngamaphilisi. Lezi zinto ezimbili ezikhuthazayo azihambi nje ngokuhambisana; kunobufakazi obuqondile bokuthi zibanxusa ukusebenza kwamanethiwekhi afanayo.

- Ukusetshenziswa kwezikhathi ezithile kususela ilungiselelo elilodwa elilindela ukuthi lesi sifundo liyibuyisele. Izikhathi zokusebenzisa izidakamizwa ezihlanganisiwe zivamise ukuba nemihla eminingi, ngamawashi amaningi, futhi zifaka ukuthatwa kwezidakamizwa okuphindaphindwe futhi nokulala okuncane - futhi uSigaba 12 kusho ukuthi ukulala okungahle kukhangezwe kungaba nomthelela ekuhlanzeni. Ngokwakhiwa, lokhu kufana nokuhlanganiswa okumibi kakhulu kwezinto ezingočaze ezichazwe kulo lonke lesi sifundo, okwenzeka ngasikhathi sinye, futhi okuphindaphindwe.

UGHB/GBL unengozi ehlukile futhi ekhulu engahlobene ne-ΔFosB: ukuthemba kungathuthuka ngemva kwamaviki ambalwa kokusetshenziswa okuqobo. Ukweqa kusebenza ngohlelo olufanayo lwe-GABA njengokuthenga kanye ne-benzodiazepines. Kungabangela ukulahleka kwengqondo, ukugqwala, kanye nezinkinga ezinkulu kakhulu okudinga ukunakekelwa okukhulu. Ukuyeka ukusetshenziswa okuqobo kwe-GHB/GBL ngendlela engenamsebenzi futhi

ngaphandle kokunakekelwa kwezokudokotela kuyingozi. Lesi yisigaba esifanayo somyalezo oqala ngaso umhlahlandlela wokuthenga—funda ngokuqinisile.

Ngeminye, ucwaningo lwezokwelapha oluxazulula ukusetshenziswa kwe-methamphetamine ehlobene ne-chemsex lubonisa ukuthi kukhona izinga eliphezulu kakhulu lezinkinga ezifana nokuduka, ukukhathazeka, i-PTSD, kanye ne-psychosis uma kulinganiswe nomphakathi jikelele, futhi lokhu kubucayi kakhulu uma umuntu udlala kakhulu. Okwengeziwe, izifundo zokwelapha ezihlanganisa i-GHB/GBL zibonisa ukuthi ukusetshenziswa kwezinto eziningi kanye nokusetshenziswa okukhulu kungabangela ukuthi umuntu ungahlali kuleli khambi lokwelapha. Lokhu kuhambisana, kodwa akuhlelwani ngokuphelele, nomkhuba we-ΔFosB okhulunywe kuleli bhulogi — kukhona eminye imininingwane ebonakalayo evela ezifundweni zokwelapha kanye nemininingwane yokwelapha.

10. Amaholide ezidakamizwa, "Ukubuyisela," kanye nokuthi kungani ukuphinduka kubuhamba ngokushesha.

Lesigaba esingesinye esibaluleke kakhulu kuleli khasi, ngoba sichaza into ethile okuningi abantu abathatha kuyo ekuhlelweni kokululama, kodwa abambalwa abayitholile: ukuhleleka ukuyeka ukusetshenziswa— "ukuhleleka ukuyeka ukuthola ukutoltolwa," "inyanga yokuyeka," "umzamo wokubuyisela ukuziphatha okuhle"—kulandelwe ukubuyela ekusetshenzisweni, futhi ukutoltolwa kubuyela ngokushesha kakhulu. Akuhlelweni ngokubuya kancane ezinyangeni eziningi njengokokuqala. Kubuya ngokushesha, njengokuthi akukho isikhathi esidlule.

[OKUSELINGISELWA] (kuyakhiwe ngohlelo lwe-chromatin olusunguliwe kwiSahluko 4, futhi kuhumushwa ekubuyiseleni—indlela eyaziwayo yokucwaninga ukubuyela emuva ezilwaneni).

Ngenxa yokuthi lokho kwenzeka, ngamazwi alula: ukuphumula ngempela kuvumela i-ΔFosB iphrotheni ukuthi idilize — le yingxenye yangempela yokubuyisela, futhi yingxenye efingqiwe kuleli khasi lesi-3. Kodwa leli khasi lesi-4 lachaza into eyodwa eyashiywa yile phrotheni ngendlela yokulahlekelwa kwayo: i-chromatin eyenziwe kabusha kuma-gene athile (ecindezelwe e-c-fos nge-HDAC1, evulwe e-CDK5/GluA2/ARC nge-BRG1), kanye nokwanda kakhulu kwezinongo zendlovu ezithintekayo kuma-neurons ekuqaleni okubuyisela umvuzo. Akukho nalokho okubuyela ngesikhathi esifanayo njengale phrotheni. Isimo esingokwezinto ezibonakalayo asibuyeli esendle ngaphambi kokuthathe izidakamizwa nje ngoba i-ΔFosB. kuyisimo esilungele ukusebenza, kodwa manje sikhululekile futhi sisezindleleni ezimile.

Uma ukusetshenziswa kwezidlo kuqaliswa kabusha, akuyona into efana nokufaka i-ΔFosB esifundweni esisha. Kunokufaka i-ΔFosB esifundweni esivele sinomkhakha wamathendevu, ukukhishwa kwezikhathi-mbili, kanye nokufinyelela kwe-chromatin okusele kusukela ngaphambilini—okuyinto eyakhiwe kanye futhi engahlukaniswa ngokuphelele. Ukwakha kabusha kwe-ΔFosB esiswini esiqinile esiqokelelwe esifundweni esilungile kungase kudinge ukuchazwa kabusha okuncane kakhulu kunokwakha okokuqala, ngoba iningi yomsebenzi wokwakhiwa kakhulu sevele sezenziwe. Lokhu ihambisana nomkhuba oyinguqulo yokuqaliswa kwezidlo ezilawulwa ngamanye amagama ekutshalweni kwezilwane, lapho Ukubuyela kokuphindaphindiwe ngemuva kokuzimisele kuguqula ukuzama ukuthola idokotela ngokushesha kakhulu kunalokho okuthathile ukwenza ukuthi uqale ukuzama ukuthola idokotela — futhi kuyisihloko esihle kakhulu esibonisa ukuthi kungani abantu abaningi bathi "Ngibuyile ngokushesha, ngiyithola ngokushesha, ngiyazi ukuthi

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Ukubaluleka kakhulu akuyona ukuthi ukuphumula kungenanzuzo—isikhathi esincishisiwe sokusetshenziswa kuyakhuthazwa, futhi noma yikuphi ukuncishiswa kokuphakama okuyisikhathi esiphelele kwe-ΔFosB kungukuphimisela okwenzeka. Okubalulekile ukuthi ukuphumula akufanele kuhlelelwe noma kuthembelwe njengokubuyela ku-zero. Isifuba siyakhumbula okuningi kakhulu kunalokho okwenzeka kule-protein, futhi ukuqala ukusetshenziswa futhi ngemuva kokuphumula kusezingeni elihilelekile lokubuyela endleleni oyilandelayo kunokuba uqale indaba entsha.

11. Ukuguga Kwamaseli kanye Nokuvuvukala Kwengqondo.

[OKUQHAMUKAYO] (izinhlobo zezilwane; indawo entsha futhi engasetshenzisiwe kakhulu kunamaSahluko 1-4)

I-ΔFosB inhlanganisela emisebenzini engaphezi ukungcola, kodwa futhi ihilela ekupheleni kwebhayoloji yekamswakama kanye nomswakama. Njengengxenye yombusho we-AP-1 (ihlanganiswe kakhulu ne-JunD), iqobo ezindleleni eziholile ekupheleni kweseli - isimo lapho iseli lithinta khona ekwenzakaleni futhi ithatha iphrofayili yomsebenzi ehlukile, evamise ukuba yindlela yokuthembeka.

- Ezinkumbulweni ezingakwazi ukwanda, ukucindezelwa okuhlala njalo noma ukugxilisa okugqamile kungadala ukuthi amaseli afake esimweni esifanele esibizwa ngokuthi "ukuvikelwa okusheshayo okubangelwe ukucindezelwa" (SIPS). Umsebenzi oqhubekayo we-ΔFosB, kanye nomunye umfihlo ofanayo (i-EGR3), uhlobene nokwanda kokukhiqizwa kwamajini okuphendula umonakalo we-DNA (i-GADD45B/G) kanye ne-p21 (CDKN1A), okungalesi simo ingabe kungaphazamisa ukuguquka kwe-synaptic futhi kunciphise ukukhiqizwa kwezinkumbulo e-hippocampus.
- Eziceli ezisengozini—amasasitrozi namakrogliya—umsebenzi oqhubekayo we-AP-1 uhlobene ne-Senescence-Associated Secretory Phenotype (SASP): amaseli eziceli adala okukhishwa kwezimpahla zokukhuthaza ukuthembeka kokuqubuka okushaywa yindlela, okungahle kuthuthukise ukuthembeka kokuqubuka okuncane eziceli eziseduze. Ukunyuka okuphakeme kwezihlabelelo zengcindezi (i-CRF, ama-glukokortikoyi) kungahle kuthuthukise kabanzi le ndima.
- Ubuhlobo abungenzi kabi kakhulu—ukusetshenziswa kanye nesigaba selengcweti kubalulekile. Ekuphathini, ukukhuliswa kwe-ΔFosB kuhlobene nemiphumela enguquko ekhuthele ekwelapheni ezimodelini zezilwane ezidala (ukutola okungcono komshini, ukuncipha kokukhuliswa kwesisindo okuhlobene neminyaka). Ezifundweni ezithile ezihlanganisa ukungqubuzana kanye nezimodelini ze-Alzheimer, ukukhuliswa kwe-ΔFosB e-hippocampus kubonakala kunciphisa ukulahlekelwa kwezeselula okubangelwa ukugxilisa, ngisho nakuthi kukhathazekile imisebenzi ethile yomlingo—lokhu kuyindlela yokuthengiselana eyiqiniso kunokuba nje into emibi.

Le ngxenye ifakiwe ukuze iqedwe futhi ngoba iyindawo esebenzayo kakhulu yokucwaningi ngale molecule efanayo - hhayi ngoba kushintsha noma yini ezahlungelenweni zokululama ngenhla. Kuyisihluthulelo esisha, esingabuthakathazi kakhulu kunokuzwelwa kwezindlela zokuzithinta ezikhunjulwe ezahlungelenweni 1 kanye no-4.

12. Yini Empompi Empelile — Ixhaswe Ngomfundvo Ofanayo.

- Ukuzinza okuqhubekayo—yindlela enkulu kakhulu, kanye ngempela into eyenza ukuthi ukwandisa kokuphuma kungaphazamiseki ngokushesha kunalokho okwenzekayo.

[ESEKHISIWE] Ukuzivocavoca ngokuzithandela kubangela ukukhuluphala kwe-ΔFosB kwi-nucleus accumbens, ngendlela ehlukene kunezokudlala izidakamizwa, kodwa ehambisana nemodeli ezilwane nekhono lokulwa kanye nokunciphisa ukufuna izidakamizwa, kungeyindlela engalungile. Iphrotheni efanayo, ekhuluphaliwe ngendlela ehlukene, ingase isebenze ngokulwa nomkhuba esikhathini esifushane.

- Ukulala - ukuhlanzwa kwe-proteasomal kuxhomekile kakhulu ekulaleni okwanele; ukuntuleka kokulala okwedlule isikhathi kungaba yinto ephazamisa ukubuyela esimweni esijwayelekile (okungabonakali).
- Ukunciphisa ukucindezela — ukucindezela okuqhubekayo kunenhlanhla yokukhuthaza ukwandisa kwe-ΔFosB ngokwayo ngohlelo lwe-HPA, okwengeza kuleyo ebanjelwe yimikhiqizo.
- Isikhathi, ngendlela engahleliwe—iphase yokuqina nokuhlala, ezivezwa kwi-Sections 3 kanye ne-4, ithatha amasonto ambalwa kuya ezinyangeni, hhayi izinsuku. Ukulindela ukuthi izinsuku ezimbili nje zibe yonke indaba kuholela ekuthini okungaba yinkinga uma ifiso liyabuyela ngemuva ngenxa yezinto ezibonakalayo—futhi, njengoba kuchaziwe ku-Section 10, ukuqala ukusetshenziswa ngaleso sikhathi kuqala ngamajethi asevele asetshenzisiwe, hhayi amasha.

Inothi.

IDFosB ichaza, ngokuchazwako, ukuthi kungani ukuziphatha okuyisiko kungaqhubeka nokudonsa umuntu kakhulu ngemuva kokuthi izizathu zokuyeka ziqaphele ngokuphelele — futhi kungani ukuphumula, noma kunjalo, akufani nokubuyisela. Akuyona yonke indaba, futhi okwamanje akunakuhloliwa ngempela kumuntu ophilayo ngobubanzi abantu abafuna, futhi akukho luthekelethi olutholakala namuhla olungakunikeza usuku oluqinisekiswe mayelana nokululama. Usebenzisa ngendlela okufanele ukuthi uyisebenzise ngayo ngamanye amacebo aluhlaza olwazi oluyingxenye ye-Recovery Kernel — njengengxenye eyodwa eqinile, ekhulayo, kukhululekile, hhayi. njengophawu.

Izincwadi ezifanele ezalwa kuleli candelo: Indlela Yokululama Ekuphuzeni, Indlela Yokululama Ekuphuzeni Kwamakhambi, Indlela Yokululama Ekuphuzeni Kwamakhambi Okwelapha, kanye ne-Complete Protocol Compendium (Ivolumu III - Izinto Ezibandakanya Ukuziphatha kanye Nezindlela Zokwelapha, kanye neVolumu I - Ukungena Ngokungathi Sicela kanye Nesisekelo Sobudlova).